President's stem cell research picks - April 2011

President's Update on Advances in Stem Cell Science

Highlights of recently published papers from CIRM grantees and other leading research teams around the world - April 2011.

First "Organized tissue" from stem cells in a dish

M. Eiraku and his team at Japan's RIKEN Center for Developmental Biology reported in in the April 6 *Nature* that they have been able to turn stem cells into a rudimentary retina in a dish.

Although differentiating stem cells into a desired cell or tissue type was once difficult, it is becoming almost commonplace. The Japanese team took this one step further creating an organized tissue, an optic cup of the retina, which develops a double wall, with pigment epithelium on the outer wall and neural retina on the inner wall.

As usual with differentiation, the medium and environment was critical to their success. They used serum?free culture of embryoid? body like aggregates and then added a gel of extracellular matrix proteins—a kind of glue for the cells. They observed that the neurons actively divided and organized into a synapse?forming structure that resembled the postnatal retina. While this work could eventually lead to the development of tissue to replace damaged retinas, it can immediately be used to study eye disease.

Two new methods use reprogramming to yield beating heart cells

- CIRM grantee Sheng Ding at Scripps Research Institute published data in the March *Nature Cell Biology* on a method that used partial reprogramming to derive beating heart cells from mouse skin tissue.

Another CIRM grantee, Deepak Srivastava of the Gladstone Institutes had previously directly reprogrammed cardiac fibroblasts to become cardiomyocytes without first taking them through a pluripotent state. In the new work, Ding first directed the cells to an intermediate state partially toward pluripotency that he characterized as a cellular transdifferentiation platform, and from that state continued to direct the cells toward cardiomyocytes. This process was much more rapid, yielding beating heart cells in 11?12 days instead of four?to?five weeks and it produced the desired cells in much higher numbers. Ding suggests this highly plastic intermediate platform could be used to derive many cell types beyond heart. One problem with the technique is the reprogramming used viral vectors and permanent genetic modifications.

- Researchers funded by the Maryland Stem Cell Research Fund at John Hopkins lead by Elias Zambidis reported in the April 8 *Public Library of Science ONE* that they were able to differentiate both embryonic and induced pluripotent stem cells into beating heart cells using transient gene modification.

Again, with differentiation, it is often all about the medium and the environment. The Hopkins team manipulated 45 different variables to come up with a cardiac differentiation system that was fast and efficient yielding nearly 95 percent of the desired cells within nine days from four hESC and seven iPSC lines. Some of the iPS cell lines were made using nonintegrating plasmids for the genetic reprogramming, making the ultimate cardiac cells much closer to tissue that could be used clinically in patients.

Another role for RNA in determining a cell's identity

CIRM grantee Howard Chang and his team at Stanford published in the April 7 *Nature* evidence that a particular type of RNA positively selects the proteins a cell produces, therefore determining its identity, or tissue type.

All cells have the same genes, but their cellular identity is determined by which genes are actually transcribed so that the protein they encode can be assembled. A number of small RNAs such as interfering RNA have been associated with silencing genes, but the Stanford team has identified the first RNA that creates a memory of gene activation turning on the gene. The regulatory molecule is one of a class called Long Intergenic Non?coding RNAs (linkRNAs). This particular linkRNA has been dubbed HOTTIP and seems to coordinate the activation of a number of HOX genes.

This type of basic understanding of the genetic workings of normal cellular function can dramatically improve researchers' ability to shift cellular development in predictable ways—which is often at the heart of creating therapies from stem cells.

Progress in turning iPS cells into therapeutic tissue that functions in vivo

- R. Perlingeiro and his group at the University of Minnesota reported in the April 2 *Stem Cell Rev* that they were able to turn iPS cells into muscle progenitors and get engraftment of the muscle tissue and improved muscle function in dystrophic mice.

The team used induced expression of Pax7, a transcription factor known to derive myogenic progenitor cells to drive the stem cells to become muscle progenitors. When these iPSderived myogenic progenitors were transplanted into a mouse model of dystrophy the mice produced large quantities of functional skeletal muscle tissue that incorporated normally in
the host muscle.

- P. Ma's group at the University of Michigan published data in the March 23 *Biomaterials* showing iPS cells could be differentiated into vascular smooth muscle cells(SMC), which could be grown on a scaffold and their SMC function retained when implanted in mice.

The researchers used trans retinoid acid to drive the stem cells to become the vascular smooth muscle. They then grew the cells on porous nano?fibrous scaffolds in vitro and implanted this tissue structure subcutaneously. In the animals they were able to detect SMC? specific markers in the tissue after two weeks suggesting this technique could eventually be a source of personalized vascular tissue for repair.

Generating iPS cells keeps getting more efficient and without gene integration

- Shinya Yamanaka, who spends part of his time at the CIRM?funded Gladstone Institutes, worked with his team at his home institution, Kyoto University, to create an efficient route to gene?integration?free iPS cells and published the method in the April 3 *Nature Methods*.

The field has been anxious to get around the permanent integration of the reprogramming factors required for early iPSC methods because of fears such integration could lead to cancer if the cells were used for therapy. The Yamanaka team had previously reported creation of integration?free iPS cells using small circles of DNA knows as episomal plasmid
vectors. But their prior method required a labor?intensive seven reprogramming factors and like the several other integration?free methods reported in recent months, was not very efficient in generating iPSCs. They tried seven combinations of reprogramming factors and discovered that one combination, with five growth?promoting factors plus one that silenced the tumor suppressor p53, yielded iPSCs efficiently. Two of the lines created were from donors who had HLA immune markers that matched 20 percent of the Japanese population, a major step toward off?the?shelf allogenic cell therapies.

- E. Morrisey and his team at the University of Pennsylvania published data in the April 8 *Cell Stem Cell* showing that microRNAs can be used to efficiently reprogram mouse and human skin tissue to create iPSCs.

Traditional reprogramming that integrates four transcription genes to induce pluripotency yields maybe 20 reprogrammed cells out of 100,000 cells. The Penn team used a microRNA cluster that is expressed at high levels in embryonic stem cells to induce skin cells to return to an embryonic?like pluripotent state. They got 10,000 iPSCs for every 100,000 cells they started with. The team reported that it appears like the microRNAs repress the repressor of the four transcription factors traditional iPSC methods try to express.

An explanation for why cells from marrow may help the heart - a bit

A team at the Harvard Stem Cell Institute lead by Richard Lee published data in the April 8 *Cell Stem Cell* suggesting why certain stem cells from bone marrow, when transplanted in or near the heart, can sometimes produce modest improvement in heart function.

Numerous human trials in post?heart attack patients using mesenchymal stem cells from bone marrow have shown modest and often transitory improvement in heart function. However, because those cells don't turn into heart cells or even survive long?term, the trials have raised many questions about how the benefit arises. The Harvard team reports that a subset of the marrow cells called c?kit+ cells are capable of stimulating adult cardiac stem cells already present in the heart to repair some of the heart attack damage.

The mice in Lee's study had lost 40 percent of heart function and gained enough improvement from the c?kit+ cells to avoid heart failure. He wrote that the goal would be to find a drug that could, like the c?kit+ cells, stimulate the endogenous cardiac stem cells to repair damage from a heart attack.

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